ANNALS OF SURGERY

VOL. XLIII JUNE, 1906 No. 6

ORIGINAL MEMOIRS.

AFFECTIONS OF THE THYROID GLAND.

A CLINICAL AND PATHOLOGICAL STUDY.[1]

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DURING the past few years as a result of the great advances in the surgery of the thyroid gland, the study of the many diseases of this organ has been placed upon an intelligent clinical and pathologic basis. There still remains, however, a lack of uniformity not only in the classification of the various lesions but also in the interpretation of their etiology and their pathologic significance. It was with the object of adding, if possible, to our orderly knowledge of the pathology of the thyroid that this study of a large series of cases was undertaken.

Material.—Since the opening of the Bender Laboratory, in 1896, a period of about ten years, material removed at operation from sixty-one cases of thyroid disease has been examined. It is upon this material, mainly from the surgical clinic of the Albany Hospital, together with three of my own cases, that this present study is based. Including, as it does, examples of all of the more important affections of the thyroid gland, with careful gross and microscopic descriptions, this group of cases offers unusual opportunities for investigation.

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[1] Read before the Medical Society of the County of Albany, February 14, 1906.

This material may be classified as follows:[1]

Class.	Disease.	No. of Cases.
I.	Simple hypertrophy	26
II.	Adenoma	9
III.	Recurrent adenoma	3
IV.	Cyst	12
V.	Metastatic thyroid tumor	1
VI.	Exophthalmic hypertrophy	6
VII.	Chronic thyroiditis	1
VIII.	Tuberculosis	2
IX.	Carcinoma	1

These lesions fall naturally into three groups,—the hypertrophies, the tumors, and the inflammations,— and should perhaps more properly be discussed in this order. Several departures however will be made in order to more clearly present the relations of the various lesions. Simple hypertrophy and adenoma as they possess, histologically, much in common, will be considered in sequence, thus affording a better opportunity for differentiation. The exophthalmic type, aside from the fact that it represents a diffuse process, bears no points of resemblance either clinically or pathologically to the simple colloid form and will therefore be considered by itself. The cysts have been found to have such close relationship to the adenomata that they may be considered with the latter.

In the study of each type of lesion, a systematic manner of presentation will be pursued as far as possible. First, a tabulated list of the cases, giving the age of the patient at the time of operation the age of onset, the duration of the disease

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[1] To these might be added, to make a classification complete, the sarcomata, the fibromata and the mixed tumors, together with acute thyroiditis, all of which are very rare affections and have not occurred in this series.

I wish here to express my thanks to Dr. Pearce for the privilege of using the material at the Bender Laboratory, and also indirectly to Dr. Blumer, whose careful records has made this study possible. Also I wish to thank the surgeons of the Albany Hospital, especially Drs. Vander Veer, Macdonald and Elting, who have allowed me access to their clinical records.

and the ultimate outcome when possible, will be presented. Following this one or more typical cases will be related in detail, with a brief clinical note and a complete pathologic study. When other cases offer points of interest or importance, not already covered in the quoted cases, attention will be directed to these special features in the general discussion. The etiologic and pathologic significance of the group as a whole will then be considered, and finally, after the consideration of each separate group, a résumé will be made of the main points in diagnosis and treatment of thyroid lesions in general.

I—SIMPLE HYPERTROPHY (COLLOID HYPERTROPHY). TWENTY-SIX CASES.

No.	Age of onset.	Age at operation.	Duration.
1	22	23	16 mos.
2	24	25	12 "
3	..	68	
4	13	13	6 "
5	..	..	
6	..	..	
7	..	30	
8	24	25	12 "
9	..	43	
10	..	42	several years
11	42	43	1½ "
12	40	43	3 "
13	16	18	2 "
14	24	27	3½ "
15	13	23	10 "
16	13	15	2 "
17	32	40	8½ "
18	44	62	18 "
19	11	18	7 "
20	..	..	
21	15	49	34 "
22	..	47	
23	36	53	17 "
24	..	..	
25	..	56	
26	..	28	

Average age at onset, 24 years; average age at operation, 36 years; average duration, 7 years, 4 months; females 21, males 3, sex not stated, 2.

Case I.—(Path. No. 05-1011.) Male, aged 18; for 7 years has had enlargement of the neck with at times dyspnœa and some prominence of the eyes noticed. His mother is said to have had the same condition.

Physical Examination.—A symmetrical enlargement of the entire neck anteriorly and laterally, but slightly greater on the right side, is seen. The enlargement extends outward and backward on either side and is felt deep under the sterno-cleido-mastoid muscle.

Operation, June 15, 1905, by Dr. G. E. Beilby. Cocaine. Transverse Kocher incision. The thyroid gland, with the exception of a portion of the upper part of the left lobe about 4x4 cm. in extent, was removed without difficulty. The right lobe is larger than the left and extends more deeply into the tissues.

Patient made an excellent recovery. In January, 1906, the patient's health was excellent.

Pathology—Macroscopic Examination: Specimen consists of a thyroid gland showing distinctly right, left and median lobes. Weight 530 grammes. Left and median lobes have been removed entire; a portion of right lobe is absent. The left lobe measures 12.5x5x4 cm., the median 4x2 cm. and the right 10x5x6 cm. The mass is definitely encapsulated, of firm consistence, distinctly lobulated and of a dark red color. The blood-vessels of the capsule are very large and tortuous. The right and left lobes are somewhat symmetrical and more or less kidney-shaped, with flattening of the posterior surfaces. The right lobe is of somewhat greater diameter anterio-posteriorly than the left. On section right lobe is seen to be grayish yellow in color and from the cut surface escapes a thick gelatinous material. It is lobulated; the lobules being composed of numerous alveolar spaces the walls of which are formed of rather firm bands of connective tissue and in which is a colloid material of a clear translucent appearance. Very many large blood-vessels are seen on section. No cysts are present. The left lobe is similar in all respects to the right.

Microscopic Examination.—Sections from four different portions of mass all show practically the same condition. In general the structure is that of the normal thyroid gland. The gland acini however, are greatly dilated and filled with a homogenous colloid material which stains with eosin. These acini for the most part are lined with a single layer of cuboidal epithelium. In many are blood-corpuscles and cholesterin crystals. The capsule of the gland is very delicate, and there is but a moderate amount of connective tissue throughout the gland substance.

Microscopic Diagnosis.—Simple colloid hypertrophy.

CASE II.—(Path. No. 97-5). Female, aged 23, single. History of enlargement of the neck in the region of the thyroid for 13 years. The enlargement has gradually increased. Recently patient has complained of dyspnœa, dysphagia and nervousness. No exophthalmus.

Operation.—November 15, 1897, by Dr. Macdonald.

Pathology.—Macroscopic Examination: Specimen consists of a lobulated mass of tissue of firm consistence, measuring 12x6x4 cm. It is divisible into two lateral lobes and a central portion, which probably represents the original thyroid gland. The surface is smooth for the most part, but in places, particularly posteriorly, is covered by vascular adhesions. The cut surface has a yellowish gray color, is irregularly divided into lobules, and is dotted here and there with cysts, containing a yellow, jelly-like material. This surface is smooth and glistening and covered with a translucent, sticky material. There are no signs of old or recent hæmorrhage into the gland substance.

Microscopic Examination.—The tumor consists of tissue having in a general way the appearance of thyroid gland. It differs from this structure only in a marked increase in the size of many of the gland acini which contains a large amount of colloid material. *Microscopic Diagnosis.*—Simple colloid hypertrophy.

CASE III.—(Path. No. 05-996). Male, aged 60. History of goitre for 18 years which, though of large size, caused no symptoms until two months ago, when severe dyspnœa and dysphagia developed.

Operation.—September 26, 1905, by Dr. Elting.

Pathology.—Macroscopic Examinations: Specimen consists of a flattened encapsulated dark red mass of tissue measuring 11x8x5 cm. having the general appearance of an enlarged thyroid gland. One surface is irregular in form and is covered by fine adhesions; the other surface shows irregular lobulations separated one from another by deep fissures. The capsule contains a rich plexus of veins. Loosely attached to this mass is another similarly encapsulated mass 6x3.5x2.5 cm. which is pinkish red in color, lobulated and the seat of numerous small cysts. The surface is covered with fine adhesions. The cut surface of the larger mass shows a greatly thickened capsule surrounding well-marked lobules which have a smooth, glairy surface, and appear to be filled with colloid material. The smaller mass on section shows a similar capsule, paler in color and with smaller, less well-marked lobules, and numerous small cysts filled with yellow blood-stained fluid.

Microscopic Examination.—Sections show structure of thyroid gland with capsule greatly thickened. The acini are greatly increased in size and number and filled with colloid. There is no increase in the interstitial substance or in the cells lining the acini.

Microscopic Diagnosis.—Simple colloid hypertrophy.

These three cases illustrate very well this type of enlargement. It is characterized clinically by symmetrical increase in size, which is usually not rapid but extends often over many years. It is true that one lobe may be larger than the other, but the essential change is a diffuse involvement, and the term "simple goitre" or "simple hypertrophy" should be applied only to those lesions which thus involve the entire gland.

Histologically, the characteristic feature is a dilatation of the thyroid vesicles, the result of the increased colloid secretion. There is lack of uniformity in the size of the vesicles, but it is rare to observe any portion of the gland which shows normal vesicles. The connective-tissue stroma in the earlier cases is often found to be somewhat scant but definite lobulations can always be made out. After the condition has existed for a number of years secondary changes may produce a rather complex picture. These are most frequently hæmorrhage into the alveoli, with associated degeneration and pigmentation in focal areas. Infiltration of leucocytes and lymphoid and plasma-cells is not infrequent. The connective tissue in cases of long standing is usually very abundant . Calcification is common as a late degenerative change. Cysts of large size in a gland showing simple hypertrophy have not been observed. Minute smooth walled cysts formed evidently by the rupture of the walls of adjacent vesicles, with fusion of their colloid contents, are commonly present.

Etiology.—It will be remembered that in the early embryonic thyroid colloid is not present in the epithelial vesicles. The colloid secretion makes its appearance at about the time of birth and first in small amounts, but with the advancing age of the child the individual vesicles show increased dilatation; the gland probably attaining its most active secretory stage during youth or early adult life. An enlargement of the thyroid at this period is very common, but it usually disappears at twenty-three to thirty years of age. This enlargement probably represents a simple hypertrophy of the organ. In explaining this condition of simple hypertrophy, then, it seems proper to infer that in a certain number of cases, instead of a subsidence of this physiologic hypertrophy, the process in an exaggerated form continues and a permanent hypertrophy is the result. In this series it is seen that while before twenty years of age only four cases came to operation, in six the age of onset was before twenty and in four others, in which the age of onset is stated, it was between twenty and thirty years, making nearly one-half of the recorded cases appearing either in youth or early adult life. Pregnancy in a few instances has apparently been the exciting cause.

In simple hypertrophy there is as a rule no symptoms except those produced by pressure upon the structures of the neck. Circulatory disturbances with extreme enlargement seem to be fairly common. Vertigo, which is frequently a symptom, is due, possibly, to pressure of the enlarged gland upon the blood-vessels of the neck. The duration of the condition varies greatly, for the patient seldom seeks advice until the pressure symptoms become severe. Mere deformity causes no concern, but when respiration or deglutition becomes difficult relief is sought. The periods of time represented in these cases vary from a few months to thirty-four years. The size to which the gland may attain also varies greatly. There seems to be no relation between the duration of the condition and the size of the gland. The case showing the most extensive hypertrophy in this series is Case I, quoted above.

In the condition of simple hypertrophy, then, three things may occur. First, there may be a subsidence of the active secretory process after puberty or during young adult life, and a diminution of the amount of colloid present with a return of the gland to its normal size. These are the cases of moderate enlargement. Second, the epithelium may cease to secrete colloid material after a certain age is reached, but fail to undergo retrogressive changes and the enlargement become a permanent one. Instances of this nature are frequent. The hypertrophy is of moderate degree causing as a rule no subjective symptoms, and but rarely demanding operation. Third, a condition similar to No. 2, in which in addition we see in later life, after a quiescence of many years, a rapid increase in the size of the already hypertrophied organ. This enlargement is apparently due to two causes—an increase in the colloid secretion, as observed in the primary enlargement, and an actual reproduction (hyperplasia) of thyroid tisssue. This latter is apparently the process present in the majority of cases. Only a portion of the gland may be secondarily affected. The following case, which clinically was considered to be malignant, illustrates this type.[1]

Case IV.—(Path. No. 05-1114.) Female, aged 53, goitre with slow growth for 17 years. First began during pregnancy. During the past seven months the enlargement has been rapid and confined chiefly to the left lobe. Dyspnœa and dysphagia marked.

Operation, October 25, 1905, by Dr. Vander Veer. Considerable difficulty was experienced in removing the gland, owing to its deep attachments.

Pathology.—Macroscopic Examination: Usual appearance of old hypertrophic gland with increase of connective tissue, degeneration and calcification in areas, but in addition a large amount of comparatively normal thyroid tissue, differing perhaps in that it has a more cellular appearance.

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[1] Under "Carcinoma" will be discussed the frequency with which hypertrophied glands of this nature undergo carcinomatous changes.

Microscopic Examination.—The sections show in general a simple hypertrophy with fairly large colloid vesicles lined by the usual epithelium. Here and there, however, are areas of small vesicles, some filled with cells and others containing a little colloid representing young thyroid tissue in various degrees of development. Small masses of epithelial cells are not infrequently observed outside of the colloid vesicle and probably represent focal zones of new thyroid tissue or compressed epithelial vesicles.

The histologic appearance in this case suggested the possibility of carcinoma. There is, however, no definite evidence of invasion of the old connective-tissue stroma by the new-formed thyroid tissue. This is a histologic picture frequently observed in cases of old simple hypertrophy in which there has occurred recent growth. Patient made a good recovery from the operation and was well six weeks later.

II.—ADENOMA; 9 CASES

No.	Age of onset.	Age at operation.	Duration.
1	..	38	
2	16	21	5 yrs.
3	37	55	18 "
4	..	24	
5	18	23	5 "
6	25	26	8 "
7	35	40	5 "
8	28	30	2 "
9	..	43	

Average age at onset, 26 years; average age at operation, 33 years; average duration, 7 years; female, 8; male, 1.

CASE V.—(Path. No. 755). Male, aged 55. Onset of tumor 18 years ago in the region of the thyroid. Has grown larger during the last two years. No symptoms except tumor.

Operation, September 26, 1904, by Dr. Elting. Excision of tumor of left lobe. The right lobe and isthmus seemed normal.

Pathology.—Macroscopic Examination: Specimen consists of an encapsulated tumor of the thyroid, measuring 8x6x3 cm. Tumor mass has been cut open. On section it presents a rough nodular surface mottled with dark red areas. Surrounding these is a brownish yellow zone and still further out a deep red finely granular zone. The lighter areas are approximately 1x.5 cm., the dark red areas measuring about 2x1 cm.

Microscopic Examination.—There is distinct hyperplasia of both glandular and interstitial tissue, the glandular elements in places being massed together and compressed, with irregular outlines; in other places dilated and filled with colloid material; in still other areas the glandular elements are atrophied with marked increase of interstitial tissue, which is highly œdematous and hyaline.

Microscopic Diagnosis.—Mixed adenoma of thyroid gland.

CASE VI.—(Path. No. 05-1207.) Female, aged 23. Tumor for 5 years. Rapid enlargement during the past eight months; dyspnœa. Tumor of the right lobe pushing the trachea and larynx to the left.

Operation, November 14, 1905, by Dr. Elting.

Pathology.—Macroscopic Examination: Specimen consists of a definitely encapsulated tumor 10x5x8x6 cm. Capsule is smooth and apparently free from adhesions. At one pole is a small irregular tumor. The capsule is very dense and fibrous. On section the tumor presents a uniform grayish appearance. Tissue is exceedingly soft and friable. No fibrous bands are seen. In the centre of the mass the tissue is disintegrated and there is found a small cavity filled with blood-stained colloid material. On section, the smaller tumor attached to one pole of the larger has the appearance of normal thyroid tissue and evidently represents the isthmus of the thyroid gland.

Microscopic Examination.—(See Fig. 1.) The general structure of thyroid tissue can be seen, but there are no definite lobulations as are found in the normal and hypertrophied gland. The thyroid vesicles, however, are greatly enlarged and filled with a homogeneous colloid material which stains with eosin. In some areas the epithelium lining the individual vesicles has disappeared and their contained colloid has coalesced, forming large irregular pink-staining masses. Throughout the colloid material is seen isolated cells and clumps of cells which stain poorly and which represent the desquamated epithelium. There are also numerous red-blood cells. When an epithelial lining is present instead of a

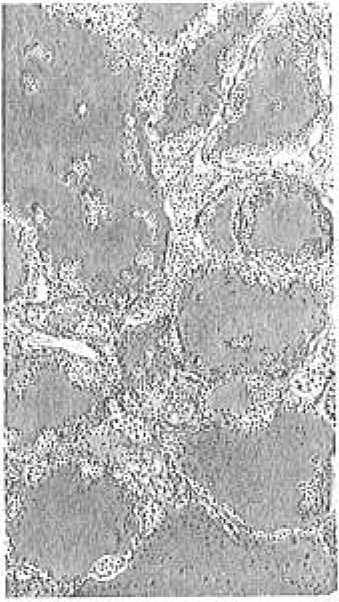

FIG. 1.—Microscopic drawing of a colloid adenoma, 4 oc. 3 obj. Leitz.

The illustration shows that the thyroid vesicles are distended with a homogeneous colloid substance in which are clumps of epithelium and isolated epithelial cells.

single layer of cells we see often several layers, and here the cells stain very poorly and have no definite arrangement. The connective-tissue stroma is very scant and the alveolar walls are delicate. There are a few small epithelial vesicles which contain no colloid and represent young thyroid tissue. The general picture is one of early degeneration.

Microscopic Diagnosis.—Colloid adenoma of the thyroid.

Case VII.—(Path. No. 64-5.) Female, aged 26. Duration of illness 8 months. The prominent symptoms are pain, dyspnœa and dysphagia.

Operation, February 20, 1899, by Dr. A. Vander Veer. No note on operation.

Pathology.—Microscopic Examination: Specimen consists of a globular nodule measuring 4x3x1.5 cm. It is completely encapsulated. Its outer surface is covered here and there with torn adhesions which are attached to the capsule. The nodule is soft in consistence. On section the cut surface bulges somewhat; it is mostly of a grey-white color and rather translucent in appearance. Scattered through it are a few whiter areas suggestive of necrosis and one or two minute hæmorrhagic points.

Microscopic Examination.—The section shows both the capsule and tumor substance. The capsule is composed of several layers of fibrous tissue, in the outermost layer of which can be seen compressed thyroid vesicles probably the result of the encroachment of the growth upon the normal gland-tissue. The tumor proper is made up of closely packed epithelial vesicles, which as a rule are empty or have only a cellular content. In this respect the tissue resembles that of the fœtal thyroid, but differs in that the cells are of a higher type. In some of the vesicles, farthest from the periphery, there is a small amount of colloid present, this probably representing the oldest portion of the growth. The connective-tissue stroma is very scant and there are no lobulations visible.

Microscopic Diagnosis.—Mixed adenoma of the thyroid gland.

Case VIII.—(Path. No. 05-95.) Female, aged 21 years, married. A tumor the size of a marble appeared in the region of the right lobe of the thyroid five years ago, two years after her last child was born, and has gradually increased in size since. Dyspnœa has been more marked of late.

Operation, January, 1905, by Dr. Elting. Ether. "The patient took the anæsthetic very badly. Resuscitation was necessary during the operation. The tumor was removed through an incision along the anterior border of the right sternocleidomastoid muscle."

Pathology.—Macroscopic Examination: Specimen consists of an encapsulated tumor measuring 2.5x2x1.5 cm., enclosed in a yellowish white capsule. On section it is fairly firm in consistence and presents a brownish white surface. Very little connective-tissue stroma can be seen.

Microscopic Examination.—Section shows a thick fibrous capsule with normal appearing thyroid tissue in its outer layer. The structure of thyroid gland can be made out, but the individual vesicles are small as a rule and contain no colloid. In a few areas the vesicles are elongated and assume a tortuous tubular shape. The connective tissue shows hyaline degeneration and œdema.

Microscopic Diagnosis.—Pure adenoma of the thyroid.

Etiology.—These adenomata comprise the solid non-malignant encapsulated tumors of the thyroid. They may arise within the tissue of the thyroid gland, without and connected with its capsule, or at some distance from the gland. They occur usually singly but in two instances in my series they occurred as multiple tumors of one lobe. In one of these were present two smaller tumors, each about 3 cm. in diameter, attached to either pole of a larger tumor 8x3x3 cm. in size. In the other a tumor of the left lobe 8x6x3 cm. in size had attached to its capsule at one pole a small nodule about 2 cm. in diameter, which macroscopically had the same appearance as the larger tumor.

As to the location, five occurred within or apparently arose from the right lobe, two from the isthmus, and one from the left lobe, and in one instance the situation was not stated. These tumors are in my experience usually of small size. The largest was 10x8x6 cm. and the smallest 3 cm. The average diameter was about 5 or 6 cm.

Clinically the adenomata are not as a rule difficult to recognize. They are hard and firm, freely movable, and generally present no symptoms except tumor. By their pressure upon the trachea or œsophagus they may produce dyspnœa or dysphagia and in two instances the extreme nervousness of the patient was ascribed to such pressure. The age of onset seems to correspond to that of adenomata in other glands of the body, occurring during youth or early adult life, when glandular activities are at their height. The age of onset was generally between 16 and 35 years; five or over one-half between the twentieth and thirtieth years. From the fact that these tumors produce no subjective symptoms, and that their growth is as a rule slow, it is often many years before the patient seeks surgical relief. It is probable that these tumors are far more common than indicated by this series, for it is only when they produce pressure symptoms or cause considerable disfigurement that the advice of the surgeon is sought.

No important etiologic factors, other than the age, can be determined. In one case, the tumor appeared two weeks after confinement.

There is nothing in the records to indicate that the thyroid gland in these cases was abnormal. Where observations were made by the operator, it is noted that the gland appeared normal.

Pathology.—The adenomata are definitely encapsulated tumors, usually smooth, but occasionally somewhat nodular or lobulated. The tumors vary considerably in consistence but are usually soft.

Two distinct varieties may be recognized, depending upon the type of vesicle. In the first, which we may designate as *pure adenoma*, the growth is found to be composed of closely-packed epithelial vesicles, containing little or no colloid and very small amount of connective tissue. Many of the acini are seen to be filled with epithelial cells. In the other variety, we have a condition in which histologically the picture very closely simulates that of simple hypertrophy. These we may designate as *colloid adenomata*. The epithelial vesicles are dilated and filled with colloid material. There is usually but a single lining layer of epithelium.

An interesting feature of these tumors is their tendency to undergo various degenerative changes. The colloid adenoma resembles somewhat histologically the simple hypertrophy, but differs, however, in some important respects. Thus the stroma is less abundant, the walls of the vesicles are thinner, and the epithelial cells lining the vesicles in the hypertrophied organ are of a lower type than those in the colloid adenoma. To make a distinction between simple hypertrophy and adenoma is easy clinically and from a macroscopic examination of the specimen but upon histologic examination distinct differences in structure are not so evident.

Briefly stated, the main differences seem to be these:

(*a*) As to the epithelium lining the vesicles. In the adenoma we find the cell tending to a columnar character, while in the hypertrophy the cells appear more compressed and assume the appearance of a cuboidal type.

(*b*) As to the contents. Colloid. In the early adenoma, epithelial tissue is the one tissue present. Small amounts of colloid are visible, but this is not seen in appreciable amounts until a later stage. In this later stage the colloid is increased markedly in amount, and approaches as to quantity the amount which is visible in the hypertrophied gland. Besides this colloid material, which in certain amounts is normally present, the alveoli may also contain desquamated epithelium and red-blood cells. In the colloid adenoma there is usually present a large number of epithelial cells within the alveolus, which stands in marked contrast to the hypertrophy where no desquamation is evident. Again in the adenoma small hæmorrhages into the alveoli are more common.

(*c*) As to stroma. In the adenoma scarcely any connective-tissue stroma is visible, the vesicles with or without colloid material being closely packed together. In the hypertrophy, however, while a number of vesicles containing considerable colloid are in close proximity, being separated by small amounts of connective tissue, the groups of vesicles are isolated and between these groups dense and rather large amounts of connective tissue are visible.

Depending upon the secretory activity of the epithelial cells of the adenomata, a complex picture may be produced.

First, All of the epithelial cells may begin to secrete actively, and varying amounts of colloid may appear within the alveolus, producing the *colloid adenoma.*

Second, All the epithelial cells may fail to secrete, and then we have a type of gland in which no colloid material is visible, resembling in many respects the type of tumor described as *fœtal* adenoma but differing in that the vesicle is not solid,—*i.e.,* made up of several layers of epithelial cells, but is merely an alveolus lined by a single layer of cells in which no colloid material is evident.

Third, A number of the cells may remain dormant while the remainder are secreting colloid material, thus presenting the picture which many authors describe as *mixed adenoma.*

Cyst Formations.—Here I wish to emphasize the fact that undoubtedly a large percentage of cysts of the thyroid have their origin in adenomata. Very frequently we find in the walls of cysts thyroid tissue resembling simple hypertrophy. Cyst formations however in thyroids that have undergone simple hypertrophy is an extremely rare occurrence. None of the cases reported in this series show aught but minute cysts formed by the rupture of the walls of a few adjacent vesicles and the coalescence of their contained colloid. The adenomata, however, appear very prone to undergo degeneration with the formation of cysts. In Case VI it was seen that the tumor presented distinct evidences at its centre of beginning cystic formation.

III.—RECURRENT ADENOMA. THREE CASES—MALE 2, FEMALE 1.

The adenomata, as has been shown in the preceding section, occur singly as a rule and do not present histologically or clinically signs of malignancy. We have, however, three cases in which there has been either recurrence at the site of operation or a subsequent appearance of a similar tumor in other portions of the gland. These were clinically considered to be malignant, and the microscopic study revealed a more or less atypical growth of epithelium.

Case IX.—(Path. Nos. 97-3 and 64-19.) Male, aged 49. Thyroid tumor appeared twenty years ago and gradually increased in size up to five years ago, causing dyspnœa and dysphagia.

Operation, February 6, 1897, by Dr. Macdonald. Removal of tumor. Five months later a similar tumor appeared in the isthmus and gradually increased in size for four and a-half years; and now presents as a firm apparently encapsulated tumor in median line of neck about 4x6 cm. in size. The lateral lobes of the thyroid show slight enlargement. The surgeon, Dr. Macdonald, considered the growth to be malignant and the entire gland was therefore removed.

Pathology.—(First operation). Macroscopic Examination: Specimen consists of a portion of the thyroid gland measuring 9x6 cm. The outer surface presents a mottled appearance, the prevailing color being red, with here and there small areas of discoloration due to hæmorrhage. The surface vessels are distended. On section the specimen shows a large empty cyst, the walls of which are thin and covered by gelatinous substance, probably colloid material. Other cysts are seen of smaller size than the one just described. They are filled with a colloid material and in some are small pea-sized hæmorrhages. Portions of the growth have undergone calcareous degeneration.

Microscopic Examination.—No definite capsule is seen. The tumor proper is made up of tissue of the same general type as that of the normal thyroid but which shows greater irregularity in the gland acini. The connective-tissue network is moderately augmented; this is evident in the size of its strands. Irregularly distributed throughout the specimen are collections of epithelial cells of the same appearance as those constituting the normal gland structure. The gland spaces are for the most part smaller than normal, though here and there dilated spaces may be seen. All alveoli contain homogeneous pink-staining material, presumably colloid; in a few hæmorrhage has occurred. There is marked hyperplasia of the epithelial cells.

Microscopic Diagnosis.—Adenomatous cyst of the thyroid.

Second Operation.—(Path. No. 64-19.) Macroscopic Examination: Specimen consists of six pieces of tissue which are evidently from the thyroid gland. The largest portion measures 7x8x4 cm. Its outer surface presents a somewhat lobulated appearance and is covered with a smooth membrane to which are attached a few fibrous adhesions. Beneath the membrane the color of the tissue is a light red. On section the tissue is of fairly firm consistence, but varies somewhat in character in the different portions. In some places it presents a semi-translucent grayish white appearance, in others it is darker in color and somewhat more opaque. Considerable portions of the specimen are made up of colloid material. Here and there are definite calcareous deposits. In one of the smaller portions which measures 7x4x2 cm. the tissue resembles that already described except that an area about 3.5 cm. in diameter is definitely hæmorrhagic. The remaining pieces which compose the specimen are similar in structure to the portions described.

Microscopic Examination.—We have here the same general type of tissue seen in the tumor removed five years previously. Some of the gland acini are greatly enlarged and filled with colloid material; others are small and have only a cellular content. The epithelium approaches the columnar type and in many places shows no typical arrangement.

Microscopic Diagnosis.—Adenoma of thyroid.

In this case the specimen first removed (97-3) is a cyst which has apparently arisen by dengeneration of an adenoma, while the second growth (64-19) presenting the same characteristics clinically, was an adenoma. The significance of this in relation to cysts will be discussed under that heading.

CASE X.—(Path. No. 64-26.) Female, aged 45. Tumor of right lobe which first appeared seventeen years ago (1888). After five years it reached the size of a lemon and was removed September, 1893, no pathologic study was made. Four years after first operation (1897) a similar tumor appeared in the left lobe and was removed six years later (Sept. 21, 1903), by Dr. Macdonald. This tumor the patient states seemed exactly similar to the first one. Both finally produced pressure symptoms upon the trachea and œsophagus, and for relief of these symptoms patient sought operation. With the second tumor there was considerable pain, and dyspnœa and dysphagia were more pronounced. The description of this tumor follows:

Pathology.—Macroscopic Examination: Specimen consists of a portion of thyroid gland measuring approximately 11x4.5x3.5 cm. Beneath the capsule except in a small portion of the end of the tumor can be seen numerous pea to cherry-sized cysts. In the centre of the specimen can be felt a hard stone-like mass the size of a cherry. On section all but a small area at one end of the specimen is seen to be filled with various sized cysts containing a clear colloid material. The wall of one of the larger cysts is completely calcified and measure 2 mm. in thickness.

Microscopic Examination.—The gland alveoli are numerous and for the most part distended by homogeneous colloid material. Some contain also desquamated cells and leucocytes many of which are loaded with pigment. The alveoli surrounding the more distended alveoli are small and arranged concentrically. Other areas show small irregularly developed alveoli. Several are irregular and without any distinct limiting wall and contain a bluish pink mucoid-like material, blood pigment and elongated connective-tissue nuclei. The interalveolar tissue shows hyaline degeneration in places.

Microscopic Diagnosis.—Adenoma with hæmorrhage and calcification and a tendency to an atypical growth of the epithelium.

About two months ago, two years after the second operation, a tumor appeared in median line of the neck and has slowly increased in size. This tumor is clinically an adenoma. There is no evidence of recurrence at the sites of previous operations. Patient's general health is excellent. The patient is considering an operation.

Case XI.—(Path. No. 97-2.) Male, aged 60. Tumor removed from the region of the right lobe of the thyroid by Dr. Macdonald nine years ago.

Pathology.—Macroscopic Examination: Specimen consists of a mass almost the exact size and shape of a kidney. The surface is irregular and in places it is covered by a distinct capsule

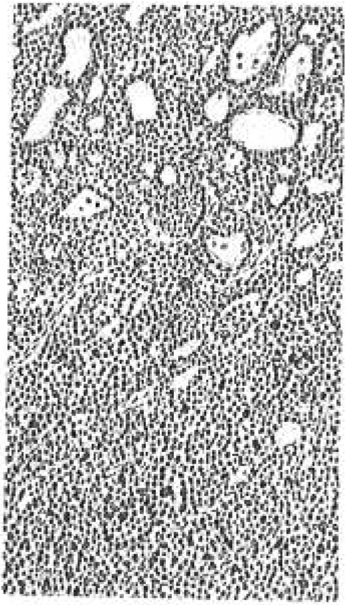

FIG. 2.—Microscopic drawing of a recurrent adenoma, 4 oc. 3 obj. Leitz.

The upper portion of the drawing shows tissue containing a few apparently normal thyroid vesicles. The lower portion shows tissue in which no normal vesicles are present, but composed of epithelial cells, having no typical arrangement, and in a few of which a large, irregular, and deep staining nucleus is seen.

which is somewhat hæmorrhagic. In other places patches of connective tissue containing large blood-vessels lie on the surface. It is somewhat lobulated and of a brownish yellow color. On section at one point is seen a cyst-like cavity containing a friable grumous material of a yellowish color, slightly viscid and apparently cell-detritus. The remainder of the tumor can be divided into a cortical and medullary portion. The cortical portion averages about 1.5 cm. in width and is distinguished from the medullary by its light color and more or less radial striation due to the presence in its substance of fine bands of connective tissue. The medullary substance is distinctly pinker in color than the cortical, and the bands of connective tissue which traverse it have no distinct or regular distribution. The consistence of the tumor as a whole is firm, the cortical substance perhaps being a little firmer. Distinct areas of calcification are present.

Microscopic Examination.—(See Fig. II.) Sections show the tumor to consist of a capsule and tumor substance. The capsule is for the most part made up of fibrous tissue. Here and there, however, it contains small collections of cells of the same type as the gland-cells, and it is evidently formed of compressed gland substance. The tumor itself is composed of a tissue of the same general type as normal thyroid tissue. It differs in the greater irregularity and shape of the gland acini. Near the capsule the connective-tissue network often runs in parallel striæ passing from the capsule into the depths. In the deeper parts of the tumor this cannot be made out. The colloid material in one or two places has undergone calcification.

Microscopic Diagnosis.—Adenoma of the thyroid.

Recurrence in same location after seven years. This second growth was an encapsulated tumor which had reached the size of a hen's egg. Specimen not saved for pathologic study.

A year after the removal of the second growth (April, 1903) there was again a recurrence which soon reached considerable size. On consulting a surgeon at this time the process was considered malignant and operation not advised. From this time until January, 1906, about one and one-half years, when patient was last seen, there has been constant increase in the size of the primary growth, which now measures 7x6 cm. in size. It is located in the right lobe of the thyroid and extends apparently deep into the neck. Near the upper pole of this tumor there is a second mass, which made its appearance about one year ago. This is entirely distinct from the older tumor, is superficial, and has no deep attachments. It is ovoid in shape, 5x4 cm. in size, and moves about freely underneath skin, which is nowhere adherent over either tumor. Patient has thus far refused operation.

We have then in this case a thyroid tumor which has returned twice after removal, the condition extending in all over a period of nine years, and in which there has developed now in the region of the recurrent tumor a secondary growth. The patient is still in fair general health but suffers from the effects of pressure. The question of carcinoma arises. The long duration would almost exclude this possibility. The growth, while of large size, is as far as can be determined, encapsulated, and affects the health of the patient only by its mechanical presence. Histologically, the first growth removed can be characterized only as an adenoma, though it does present an unusual picture, similar to that in the other two cases described in this group. An interesting feature is that in all of these cases the patients are now over 40 years of age. In one the onset of the first growth was at 51 and in the other two, one at 29 and the other at 32 years of age, thus differing from the usual history of adenoma.

IV.—CYSTS. 12 CASES.

No.	Age of onset.	Age at operation.	Duration.
1	10	16	6 yrs.
2	21	26	5 "
3	..	27	
4	17	26	9 "
5	38	42	10 "
6	33	41	8 "
7	36	43	7 "
8	15	24	9 "
9	25	33	8 "
10	19	20	18 mos.
11	49	49	4 "
12	39	43	4 yrs.

Average age of onset, 27 years and 6 months; average age at operation 32 years and six months; average duration of disease, 6 years; females 7, males 3; sex not stated 2.

We recognize three main types of thyroid cysts, *simple, hæmorrhagic,* and *adenomatous cysts.*[1]

Simple Cysts. Three cases.

CASE XII.—(Path. No. 06-197.) Male, aged 16 years. When six years of age his parents noticed a small lump about the size of a hickory-nut in the region of the left lobe of the thyroid. This increased very little in size until four years ago, since which time there has been slow but gradual enlargement. There is no exophthalmus or tremor, but the boy is of a nervous disposition.

Operation, January 22, 1905, by Dr. Beilby. Anæsthetic, cocaine. In the region of the left lobe of the thyroid is found a smooth, ovoid tumor about 5x9 cm. with its larger diameter extending from the thyroid cartilage towards the ear. No lobulations can be made out. The tumor is very tense and no definite fluctuation can be determined. It is attached to the larynx and moves up and down perceptibly on swallowing. The cyst was excised without rupture The thyroid tissue about the cyst appears normal.

Pathology.—Macroscopic Examination: Specimen consists of a cyst of the thyroid gland measuring about 6x9 cm. in size. Its outer surface is smooth and only at one pole can thyroid tissue be seen. On opening the cyst the walls are found to be very thick and fibrous. The contents of the cyst is a brownish translucent fluid with numerous oil-globules floating about in it. The inner surface of the cyst-wall is very white and fibrous and is covered with many flakes of fibrin and some atheromatous patches. One small area of thyroid tissue 1x1.5 cm. projects from the inner wall of the cyst.

Microscopic Examination.—Cyst-wall: outer layer of loose fibrous connective tissue with blood-vessels and a very cellular central zone. At first glance these cells look like lymphoid cells, but the presence here and there of small amounts of colloid material leads to the conclusion that they represent greatly compressed thyroid vesicles with atrophied epithelium. The next layer is the inner wall of the cyst, which is composed of loose lamellæ of tissue and masses of blood-corpuscles, suggesting an organized blood clot.

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[1] In addition to these, occur the small multiple cysts found with great frequency in the simple hypertrophic gland. They never attain any great size and are undoubtedly caused by the coalescence of two or more distended vesicles with fusion of their colloid contents. Clinically, they never produce any symptoms and are only of pathologic interest.

Microscopic Diagnosis.—Simple cyst of thyroid.

At present, one year after operation, patient is perfectly well.

This is the type of a thin-walled cyst. They occur in glands that are apparently normal. The cyst-wall is composed of compressed thyroid tissue. The inner wall is usually smooth and fibrous but may be lined with a mass of epithelial cells. The contents is usually fluid but varies both in color and consistence, the color depending on the amount of blood and the consistence on the admixture of colloid.

Hæmorrhagic Cysts. One case.

The following case, illustrating this type, is perhaps almost unique.

Case XIII.—(Path. No. 195.) Male, aged 41. Eight years ago patient fell backward down stairs. Noticed at once, following the fall, a swelling in the region of the right lobe of the thyroid gland. This increased in size but little until a few days previous to operation, when a rapid enlargement occurred. This was accompanied by a constant dull pain for which the patient sought advice.

Operation, March 16, 1904, by Dr. Elting. Nitrous oxide and ether. Excision of the right lobe of the thyroid. 50 c.c. of brownish fluid was evacuated from the cyst during its removal.

Pathology.—Macroscopic Examination: Specimen consists of an encapsulated mass, evidently comprising the entire right lobe of the thyroid gland. It measures 10x5x4 cm. On section a large cavity is found from which was evacuated 50 c.c. of reddish brown fluid containing necrotic tissue. The necrotic material is both free in the cavity and adherent to the walls of the cyst. Here and there in the walls are found calcified areas, none larger than 5 mm. in diameter. The wall of the cyst averages about 5 or 6 mm. in thickness.

Microscopic Examination.—Sections show the cyst-wall to be composed of thyroid tissue, in general fibrous, but in some areas quite normal. There are areas of hæmorrhage and necrosis. In these areas and surrounding them is an extensive infiltration with polynuclear leucocytes, though in general the tissue is infiltrated with lmyphoid—and plasma-cells. The picture everywhere presented is that of chronic inflammation with tissue degeneration and focal areas of necrosis. The type of thyroid vesicle where it can be made out is that of the normal gland.

Microscopic Diagnosis.—Hæmorrhagic cyst with chronic thyroiditis, hæmorrhage and necrosis.

Hæmorrhage has always been assigned as an important factor in the production of thyroid cysts. The presence of hæmorrhage, recent or old, in cyst contents or its walls is an almost constant observation. It seems probable however that this is much more commonly a secondary process than the true etiologic factor. That a primary hæmorrhage, produced either by violent trauma, or the rupture of a small blood-vessel from any cause within the substance of the thyroid gland, is capable of producing later a cyst there can be no doubt.

Adenomatous Cysts. Ten cases.

That the adenomata play such an important rôle in the production of cysts seems not to have been generally recognized. In this series, 70 per cent., or 10 of the 14 cases, present evidence of having arisen from this type of tumor.

Case XIV.—(Path. No. 05-010.) Female, aged 26. Tumor of neck nine years, gradual increase in size, more rapid during the last year. Dyspnœa and tachycardia on exertion. Pulse constantly 104-106. Marked harshness of voice. Complains of headache and pain in right ear. Tumor is situated in median line and moves with deglutition.

Operation, July 17, 1905, by Dr. Beilby. Cocaine. Transverse incision. Excision of cyst of isthmus. The remainder of the thyroid gland appeared normal.

Pathology.—Macroscopic Examination: Specimen consists of a thick walled cyst of the thyroid which was removed at operation without rupture. It is nearly globular in shape but slightly flattened in its anterio-posterior diameter. It measures 7.5x5.5 cm. Its capsule is of a pink color, very delicate and easily torn. The blood-vessels are large and tortuous. It is rather soft and fluctuant. On section it is found to contain a brownish bloody fluid. This cavity is approximately 4.5x3 cm. in size. The wall of this cyst measures from 5 to 15 mm. in thickness and seems for the most part to be composed of apparently normal thyroid tissue. There are some areas, however, which resemble glandular hyperplasia. Again other areas show hæmorrhage and necrosis. Blood-vessels are large and numerous.

Microscopic Examination.—Section through cyst-wall shows a thick capsule, which has apparently been formed by compression of thyroid tissue. Scattered throughout are many normal thyroid cells and in some areas are acini filled with colloid material and lined with cuboidal epithelium. From this capsule strands of connective tissue extend to the deeper portion of the cyst wall and form a definite connective-tissue framework, presenting somewhat the histologic structure of thyroid acini. These spaces, however, are packed with what are apparently desquamated epithelial cells. A few normal acini are noticed, which are filled with colloid material. Other sections show in addition free masses of red-blood corpuscles, and marked hyaline degeneration of the connective tissue.

Microscopic Diagnosis.—Cyst in a *mixed adenoma.*

At present, eight months after operation, the patient is in excellent health. The huskiness of her voice has largely disappeared, her pulse rate has dropped ten to twelve beats per minute, and she is not so nervous as before operation.

CASE XV.—(Path. No. 64-23.) Female, aged 26. Has had a tumor in the right side of the neck in the region of the thyroid for five years. Tumor first appeared during first pregnancy. There has been a gradual slow increase in size up to three years ago, when after the birth of her second child the growth became more rapid.

Pathology.—Macroscopic Examination: Specimen consists of a globular cystic mass 5x3.3x2.5 cm., the outer surface of which is smooth and encapsulated. On section the cyst contents are found to consist of a brownish fluid. The cyst wall is smooth. The cyst originates in the thyroid gland, and to its outer surface fragments of normal thyroid-tissue are adherent.

Microscopic Examination.—The capsule is composed apparently of compressed thyroid alveoli. Within the capsule proper the tissue has the structure of thyroid and very slightly approaches the characteristic fœtal type of gland. No colloid is visible.

Microscopic Diagnosis.—Cyst in a pure adenoma.

CASE XVI.—(Path. No. 97-4.) Female, aged 20; has had a tumor in the region of the isthmus of the thyroid for eighteen months.

Operation, October 19, 1897, by Dr. A. Vander Veer.

Pathology.—Macroscopic Examination: Specimen consists of an oval piece of tissue 4.5x3.5x2.5 cm. It is for the most part cystic, the cystic contents having been removed, leaving a cavity which occupies about two-thirds of the tumor, the upper third consisting of a solid mass of tissue. The outer surface of the tumor is moderately smooth, but here and there are the remains of adhesions. The cyst-cavity is the size of a walnut and its walls are thin, averaging about 1 mm. in thickness. The inner surface is very irregular, and is traversed here and there by raised bands. The color varies from pinkish to grayish white. Secondary cysts varying from those the size of a pin-head to those the size of a pea can be made out in the walls. They contain a mucilaginous yellowish brown fluid. In places on the inner surface of the cavity are areas of calcareous deposit. The solid portion of the tumor is only moderately firm in consistency and measures 2x1 cm. Its cut surface is of a yellowish gelatinous appearance. It contains a number of small cysts filled with fluid, which varies in color from a light to a dark brown.

Microscopic Examination.—The tumor on section presents varying appearances. In some places it has the ordinary appearance of thyroid gland structures, being made up of cavities of various sizes, containing colloid materal, between which are cellular bands of tissue. This appearance is confined particularly to the portion of the tumor furthest removed from the cyst cavity. The walls of the cyst-cavity are made up, for the most part, of a firm solid tissue, composed of a basement substance containing numerous epithelial and spindle shaped cells. In this substance are to be seen the compressed remains of the thyroid alveoli and also a very large number of cells containing a yellowish brown pigment, evidently changed blood-pigment. At one point are present in the tumor a number of wedge-shaped spaces, the walls of which are formed by the tumor-tissue. In these are occasional spaces representing a deposit of crystals, presumably cholesterin. The cells about these spaces are multinucleated, apparently foreign-body giant-cells.

Microscopic Diagnosis.—Cyst in a colloid adenoma.

It will be recalled that in discussing the adenomata we recognized two types of thyroid vesicles,—one large and containing colloid, and the other smaller in which no colloid was visible; also a third variety, combining the characteristics of these two. In the walls of these cysts we find a histologic structure which exactly corresponds to one or the other of these types. As we might perhaps expect, the colloid adenoma is the variety which most frequently undergoes cystic degeneration. Five, or one-half, of the cysts in this series were of this type. In only one could no colloid be seen in the tissue of the cyst-wall. Four were of the mixed variety. Aside from the histologic evidence of the production of cysts from solid adenomata, we have in certain of the cases a gross appearance indicating beyond doubt that the tumor was originally an adenoma and that degeneration has taken place with a resulting cyst formation. Of importance in this connection is the observation of cholesterin crystals indicating fatty transformation of the epithelial elements. If the process is an early one the cysts may be only of small size and the structure of the adenoma still be retained.

As the degeneration advances and the fluid contents of the cyst is increased in amount, there is compression of the alveoli and later many of the cells may atrophy and the stroma undergo various forms of degeneration, giving widely varying and very complex pictures. The inner layer of the cyst may then be said to be composed of the remains of the adenomatous tissue, while the wall proper represents the fibrous capsule of the original adenoma, and the outer layer, the stroma and compressed alveoli of the surrounding thyroid-tissue. With the enlargement of the cyst and its encroachment upon the surrounding normal thyroid-tissue we often get a lamellated appearance. These lamella are as the result of the successive compressions of the normal gland-tissue, with subsequent atrophy of the epithelial structures, leaving only the stroma and alveolar walls. Thus fibrous bands of varying thickness appear. Between these layers are often seen normal thyroid vesicles, and vesicles in various stages of atrophy.

The histogenesis of these cysts may be said to be as follows: In the beginning we have an encapsulated adenoma composed of cells which present no colloid secretion. As the growth continues colloid material is secreted and a coalescence of these colloid vesicles in the centre of the tumor to be seen. Hæmorrhage occurs and we have a cystic cavity filled with bloody colloid material. The fibrous capsule of the original adenoma forms the wall of the newly-formed cyst. As the degenerative process continues and the contents of the cyst increases the tumor necessarily becomes larger and pressure is exerted on the surrounding normal tissue, causing atrophy of apparently normal vesicles. As in long continued degenerative processes occurring in other tissues, lime salts may eventually be deposited in the wall of the cyst giving extensive calcified areas.

V.—ABERRANT OR METASTATIC THYROID TUMORS WHICH ARE HISTOLOGICALLY BENIGN BUT CLINICALLY MALIGNANT. ONE CASE.

CASE XVII.—(Path. No. 88-68.) Male, aged 65 years. Family and past history not important. Six months ago first noticed a fulness of right side of face and difficulty in breathing through right nostril. Tumor has increased in size rapidly and has been accompanied by considerable pain. At present there is complete occlusion of the right nostril and bulging of right eyeball with inflammation of conjunctiva, and obstruction of tear duct. At the operation by Dr. Vander Veer the antrum of Highmore was opened but only a small portion of the growth was removed. Its extensive character made a complete removal impossible. The clinical diagnosis was sarcoma of antrum.

Pathology.—Macroscopic Examination: Specimen consists of an irregular mass of tissue removed from the upper jaw. There are one or two pieces of bone, the remainder of the tissue being of a grayish white color and having the appearance of granulation tissue.

Microscopic Examination.—The sections indicate that the tissue is that of the thyroid. Two definite pictures are presented. First, large alveoli filled with colloid, lined usually by a single layer of cubical epithelium, and containing throughout the colloid substance many desquamated epithelial cells which take the stain rather poorly. Second, areas showing epithelial hyperplasia but less tendency to colloid secretion, giving the tissue a more solid cellular appearance. On careful examination of these cellular areas they are found to be composed of closely packed thyroid vesicles, some of fair size but filled with cells which approach a columnar type. Hæmorrhages into the alveoli are frequent. Connective tissue stroma is very scant. The tissue shows signs of inflammation in places, containing a number of polynuclear leucocytes.

Microscopic Diagnosis.—Aberrant or metastatic thyroid tumor.

For the further history of the case I am indebted to Dr. Merritt, of Cherry Valley, who writes me that the growth increased very rapidly after the patient left the hospital and finally involved the right eye. The bony structures he thinks were extensively involved as some of the teeth and a portion of the superior maxilla were lost during the course of the disease. To the best of the doctor's recollection and that of the patient's friends, there was no hypertrophy or tumor of the thyroid gland, either previous or subsequent to operation.

To establish a positve diagnosis of *metastatic adenoma of the thyroid,* we must necessarily have at least clinical evidence that a primary adenoma existed in the thyroid gland. This evidence is wanting. If such an adenoma existed it was so small as to escape notice. Whether or not such a primary tumor existed the case is of equal interest.

There are now in the literature records of about 20 cases of tumors apparently metastases from the thyroid, which were histologically benign. As in a number of these instances there has been no apparent primary thyroid lesion, these cases have been considered as *metastases from normal thyroid tissue.* Where a thyroid lesion has been observed it has been that of simple hypertrophy or adenoma, and the metastatic tumor has had a similar histologic structure. These metastases, which may be single or multiple, have occurred most frequently in bone and have often been removed under the supposition that they were primary growths. Aside from the fact that these tumors are probably of metastatic origin they present as a rule no other indication of malignancy. Frequently, however, they have been known to recur after removal and a number of cases have thus resulted fatally. Therefore the important question arises, are not these tumors malignant and should they not always be considered as such by the surgeon?

In the case I report the tumor presented clinically every indication of malignancy. Its invasion of tissue was rapid and death was caused in eight months after its onset. As there never was observed any hypertrophy or tumor of the thyroid gland, we can only assume that if this was a metastatic tumor the metastasis was from normal thyroid tissue. As will be noted, however, in the microscopic study, the growth was histologically a thyroid adenoma and of the type we have described as mixed adenoma.

In the case reported by Oderfeld and Steinhaus[1] the first tumor observed was in the frontal bone. This was removed and histologically found to have the structure of normal thyroid. The patient was again seen after an interval of six months, but no recurrence was evident. After about a year there was a recurrence and also other similar tumors made their appearance, one in the temporal region and one at the sterno-clavicular articulation. Clinically these tumors were considered to be malignant. At the request of the patient the one in the temporal region was removed. This presented a similar structure to the one removed from the forehead one year before. The patient died a few weeks later. Before death a thickening of the under half of the right lobe of the thyroid was noted. A complete autopsy was not permitted, but all visible tumors were removed together with the thyroid gland. Within the substance of the right lobe of the thyroid was found a small nodular thickening 2cm. in diameter, The remainder of the thyroid appeared normal. The tissues were all carefully sectioned and examined, the authors expecting to find carcinomatous degeneration, but the structure throughout the tumor of the thyroid and the other isolated tumors of the head and neck were uniformly the same and as they observe had the exact structure of normal thyroid tissue. They regard the small thyroid nodule as the primary tumor and the tumors of the head and neck as metastases.

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[1] Centralb. f. allg. Path. u. path. Anat., 1903, xiv, 84.

Etiology.—The fact that we have in these metastatic tumors structures similar or almost identical to the tissue found in the normal gland lends special interest in the etiology of these tumors. In its consideration several factors may be taken into account.

First, Origin from *misplaced embryonal tissue.* The theory which has been advanced by Conheim in which he regards the etiology of malignant growths as due to misplaced embryonal cells might be applied to tumors of this class.

Second, Origin from *aberrant or accessory thyroid.* Murphy in a recent article[2] calls special attention to a group of accessory thyroid glands which he frequently finds at the base of the tongue and which he classified as the superior group. He records 39 cases. In only three is there a note upon the histology of the tumor. Two presented the appearance of "normal thyroid," and one of "colloid goitre." In six, or 15 per cent. of the cases there was recurrence after removal but no other signs of malignancy.

Third, *Propagation of bits of thyroid tissue through the circulatory system.* It is a well-known fact that certain tissues, especially young embryonal cartilage, when transplanted into different tissues of the body or when injected into the circulatory apparatus are apparently nourished and in certain instances continue to grow. An apparently analogous condition is true in regard to the thyroid-gland tissue. Portions of this gland have been excised and immediately transplanted into another animal of a foreign species. The tissue not only has remained alive but has apparently continued to produce its normal secretion. Although no proof is at hand, it is possible that these metastatic tumors could result from small particles of thyroid tissues which had found their way into the circulatory apparatus and had been transferred to distant portions of the body. In an organ as vascular as the thyroid such a condition is not inconceivable especially under conditions of trauma.

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[2] Jour. of the Amer. Med. Assoc., 1905, xlv, 1854.

As is well known metastases from tumors of the thyroid, like those of the prostate, occur most commonly in bony structures.

VI.—EXOPHTHALMIC HYPERTROPHY. SIX CASES. ALL FEMALES.

No.	Age of onset.	Age at operation.	Duration.
1	28	29	16 mos.
2	25	26	1 yr.
3	20	21	1 "
4	24	27	3 "
5	28	43	15 "
6	44	46	2 "

Average age of onset, 28; average age at operation, 32; average duration of disease, 3 years and 10 months.

Result.—In two cases death occurred, one (case No. 3) on the table at the end of operation as a result of the anæsthetic; the other (case No. 2) died seven days after operation, with the symptoms of extreme hyperthyroidization. The remaining four cases have been either entirely cured or greatly benefited by the operation. Case No. 1, four years after operation, is well and all the symptoms have been relieved except slight prominence of the eyes which remains. The portion of the gland that was left at operation is now distinctly palpable.

Case No. 4, one year and two months after operation: the symptoms are all relieved and the patient is able to pursue his work. Before operation exophthalmos, tachycardia and nervousness were marked. Case No. 5 is well ten months after operation. Case No. 6: operation was done but one month ago. The condition of the patient is improved.

CASE XVIII.—(Path. No. 64-25.) Female, married, aged 26. Complains of enlargement of neck, poor sight and some difficulty in breathing. Onset one year ago; first symptom enlargement, followed by exophthalmus. Thyroid gland now presents symmetrical enlargement; exophthalmus very pronounced, marked tremor of hands. Systolic murmur heard over base of heart; not transmitted. Heart not enlarged. Pulse 140.

Operation, June 24, 1903, by Dr. A. Vander Veer. Ether anæsthesia. Both right and left lobes were removed. For three or four days after operation the pulse ranged between 130 and 158, temperature between 100 and 102 F. Delirious at intervals. Death on the seventh day.

Pathology.—The gross description merely contains the statement that the specimen consisted of two masses of glandular tissue, one measuring 8x4x2 cm. and the other 5x4x1.5 cm.

Microscopic Examination.—(See Fig, 3.) Sections 1, 2 and 3 all show the lobulated structure of the thyroid gland. There is an increase in the interlobular connective tissue. The vesicles composing the lobules are very irregular in size and shape. The colloid material in many of the vesicles has been entirely replaced by epithelial cells. Instead of a single layer of epithelium lining the individual vesicles, we see a number of layers, this proliferation of cells often producing invaginations or papillary projections into the cavity of the vesicle. In certain areas this proliferation of cells has advanced to such an extent as to completely fill the vesicle and we have entire lobules presenting a solid cellular structure. The cells are of a high columnar type. There is lymphocytic infiltration in areas.

Microscopic Diagnosis.—Advanced and diffuse exophthalmic hypertrophy.

CASE XIX.—(Path. No. 763.) Female, single, aged 21. Enlargement of thyroid for one year, more marked on right

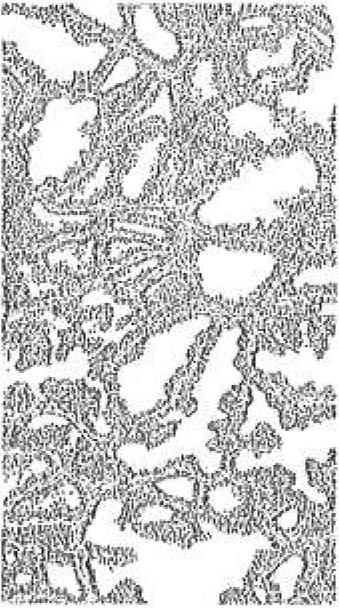

FIG. 3.—Microscopic drawing of an exophthalmic hypertrophy (exophthalmic goitre), 4 oc. 3 obj. Leitz.

In this drawing the hypertrophy is indicated by the proliferation of the epithelial cells lining the vesicles and the papillary projections into their lumen. In places some of the vesicles have been compressed by the hypertrophy of the surrounding epithelium.

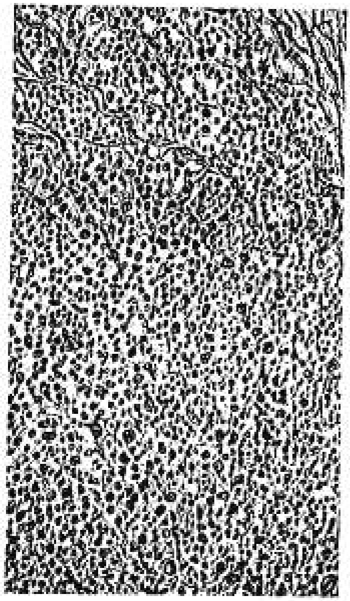

FIG. 4.—Microscopic drawing of a section of thyroid which presents in other areas a definite picture of exophthalmic hypertrophy, 4 oc. 3 obj. Leitz.

(See microscopic description.)

side. Exophthalmus, tremor and tachycardia pronounced. As patient steadily grew worse under medical treatment, operation was advised.

Operation, September 28, 1904, by Dr. Elting. Ether anæsthesia. Excision of right lobe and isthmus. Left lobe not removed. The patient died on the table at the end of operation.

Pathology.—Macroscopic Examination: Specimen consists of two pieces of tissue, measuring respectively 6x4.5x3 cm. and 3x2.5x2 cm. in size. Both are of similar structure. The larger is somewhat lobulated and is encapsulated except on one surface, near the upper pole, where there is a raw granular surface corresponding in diameter to the smaller piece. Both masses are more or less nodular and on section have a pinkish white granular appearance. There are several cysts 0.5 to 1 cm. in diameter containing straw-colored grumous fluid. The surface presents rather round or oval areas, each being somewhat distinct from the other.

Microscopic Examination.—The sections present an unusual picture for exophthalmic hypertrophy. They have in general a definite lobulated glandular appearance. In many lobules the proliferation of epithelial cells has progressed to such an extent as to entirely obliterate the characteristic thyroid gland structure, giving solid epithelial masses. The walls of the individual vesicles have disappeared, evidently as a result of pressure. In one such area (see Fig. 4) there is in addition an unusual change in the cell morphology. As seen in the microscopic drawing, the cells are very large and irregular in shape and in this regard suggest very strongly malignant transformation. In one section, evidently representing the wall of the small cyst mentioned above, the hypertrophy is not so far advanced and hyperplasia of the cells with papillary projection or invagination of the epithelial layers into the cavity of the vesicle is seen, representing more the picture we recognize as that of exophthalmic hypertrophy. The colloid material except in a few places has disappeared. In the study of these sections one is impressed with the possibility of the association of exophthalmic hypertrophy and carcinoma.

CASE XX.—(Path. No. 05-1376.) Female, single, aged 46. For six years headache, extreme nervousness and dizziness at irregular intervals. Two years ago onset of exophthalmus, tachycardia and tremor. Four months later observed enlargement of thyroid gland. This enlargement is symmetrical and well marked.

Note on physical examination.—Patient is a rather slightly built woman, rather poorly nourished and anæmic. Areas of discoloration of skin on left cheek and backs of both hands. Exophthalmus definite but not of an extreme degree. Sight has failed rapidly. Pulse regular, of even tension, 96 per minute. On admission to hospital it is recorded as 90. Thyroid gland shows a nearly symmetrical enlargement, left lobe a little larger than the right, measuring about 8.5x5 cm. and is moderately firm.

Operation, December 29, 1905, by Dr. Elting. Ether; excision of left lobe and isthmus.

Pathology.—Macroscopic Examination: Specimen consists of what is apparently the left lobe and a portion of the isthmus of the thyroid gland, which have been removed in one piece. The outer surface has a pinkish-yellow mottled appearance. It is covered by a rather delicate fibrous capsule, which has been torn in places and adheres by firm hair-like adhesions. The surface has a distinct lobulated appearance, the lobules varying in size from 0.5 to 2 cm. Several minute cysts 1 to 2 mm. in diameter are seen upon the surface. The tissue has a rather firm feel, and is very nodular. Section has been made through one area where near the surface a cyst has been opened. This cyst is 1.5 cm. in diameter and contains some thick, viscid, translucent material. On section the cut surface presents a reddish-yellow mottled appearance. Lobulations are definitely seen. These vary in size from 1 mm. to 1 cm. and are of widely different shape. The connective-tissue surrounding the lobules can be seen as distinct white bands. It seems more abundant near the centre and in the posterior part. Within the lobules can be seen minute translucent areas, which presumably are thyroid vesicles filled with colloid. The entire lobe as far as determined by section has this appearance. In the isthmus are areas of a more distinct red appearance. The lobules are firm and definite translucent areas cannot be seen. The appearance here approaches more nearly that of normal thyroid tissue.

Microscopic Examination.—A series of sections show two definite processes. There is seen to be in the majority of the sections a marked increase in the size of the alveoli and in the amount of colloid present. In certain lobules this is much more pronounced, and suggests a simple hypertrophy, differing perhaps only in the tendency of the cells to assume a higher type in many of these large colloid alveoli. In other areas there is cellular proliferation with diminution or disappearance of the colloid material. The increase in the number of epithelial cells is very great while their approach to the columnar type is not so marked. An alveolar arrangement is frequently difficult to make out. Section through the wall of the small cyst, noted above, shows it to be in the centre of a minute encapsulated adenoma. The connective tissue of the gland is moderately increased in amount and there is considerable lymphocytic infiltration in areas.

It seems, then, that we may recognize two forms of exophthalmic hypertrophy; in the one form the disease begins in an apparently normal gland and the process is symmetrical, so that histologically we find everywhere the type of lesion so well illustrated in Fig. 3. Clinically in this form we recognize as a rule a very symmetrical enlargement of the gland, though one which never attains great size. The disease is of comparatively short duration, patients dying as a rule in from one to three years if untreated. The well known symptom-complex of the disease,—enlargement of the gland with exophthalmus, tachycardia and tremor,—is invariably present. In the other form the exophthalmic process is secondary or associated with some other type of thyroid affection. In three, or one-half, the cases in this series an associated simple colloid hypertrophy was found. The cases in this series illustrating this type are Nos. 4, 5 and 6.

This form is characterized clinically by a longer duration, by a greater increase in the size of the gland, and by lesser severity of the symptoms. These cases, however, all had exophthalmus, tachycardia and nervousness of greater or lesser severity. In Case V, while the enlargement of the gland was of 15 years duration, the symptoms of exophthalmic goitre had developed more recently. In the other two cases these symptoms were present from the onset.

The histologic picture also differs. Instead of a uniform process, as in the former group, we see the exophthalmic hypertrophy only in foci or in various lobules scattered throughout the gland. In the cases where this hypertrophy is observed it is of a lesser degree. Other investigators have also recently called attention to the fact that exophthalmic hypertrophy is frequently associated with various pathologic conditions of the thyroid, as cysts, adenomata and carcinomata, and that these may be the unproduced atypical exophthalmic goitre symptoms. Usually there is present the nervousness, tachycardia and tremor of varying degree while the symptoms of exophtalmus may be wanting.

In typical cases of exophthalmic goitre, which present the well-known symptom-complex, all writers agree that the histologic changes found in the gland are definite and constant. They have been characterized as a true hypertrophy. They very closely resemble the compensatory hypertrophy which is seen in the remaining portion of the thyroid gland after its partial excision, and which in this manner has been so frequently produced experimentally in dogs. Briefly the changes are (1) a change of the epithelium from a low or cuboidal type to a high cylindrical form, (2) a gradual disappearance of the colloid material which seems to be one of the earliest evidences of beginning hypertrophy, (3) alteration in the size and form of the alveoli due to the hyperplasia and infolding of the epithelium, (4) increase in the vascular supply and in the connective tissue stroma.

As we have noted however in cases in which the symptoms are atypical no such definite changes are observed. We may see only in foci evidences of this process. It may amount simply to a change in the size and form of the cell, and perhaps instead of a single layer of epithelium lining the alveolus there may be two or more. There may be said to be, however, in all cases evidence of proliferation of cells with increased activity. Whether or not we shall be eventually forced to the conclusion that all the various affections of the thyroid gland characterized by cellular proliferation give rise to the symptoms, more or less complete, of Graves' disease is a matter which requires further study.

As to the pathogenesis of this affection nothing can be said to have been as yet definitely established. The main dispute is still whether the disease is of nervous origin or has its basis in an abnormal condition of the gland itself. The majority accept the latter view, and hold that the disease is a manifestation of an excessive or perverted secretion of the thyroid epithelium. This seems the most rational supposition and it is borne out by certain facts,—viz., the similarity in the histology of the compensatory hypertrophy and the exophthalmic variety; the relationship between the advancement of the hypertrophy and the duration and severity of the clinical symptoms; and the beneficial effects that are produced by removal of a portion of the hypertrophied gland. What relation if any the parathyroids have to exophthalmic goitre has not been determined. In none of these cases were these bodies examined. The changes that have been described are not at all constant.

In regard to the age of onset, the cases of this series correspond closely with those of other observers. By far the greatest number appear between the ages of 20 and 30, five out of six cases are recorded above. In one case, however, the age of onset was stated as 44. An onset before puberty or after 40 is rare. The disease is much more common in females than males, the proportion as variously stated ranging from 3 to 1 to 17 to 1.

VII.—CHRONIC THYROIDITIS. ONE CASE.

Case XXI.—(Autopsy No. 0-283.) Autopsy April 18, 1900, by Dr. Blumer. Female, aged 40. No clinical history.

Anatomical Diagnosis.—Sclerodema with pigmentation of the skin affecting the face, posterior part of the trunk and extremities. Acute sero-fibrinous pericarditis, with acute myocarditis and diffuse interstitial myocarditis. Double hydrothorax with acute fibrinous pleurisy on the left side. Acute bronchitis with emphysema of the lungs and atelectasis of the lower lobes. Chronic passive congestion of the liver. Acute infectious nephritis. Chronic interstitial thyroiditis. Chronic interstitial mastitis. Tuberculosis of a bronchial lymph-gland. Small ulcers over the internal condyles of the humeri.

Pathology.—Macroscopic Examination: The thyroid gland is small, firmer and somewhat grayer in color than normal. It contains apparently an increased amount of connective tissue.

Microscopic Examination.—Marked changes in the gland are seen. These take the form of a great increase in the interstitial tissue of the organ, producing compression and atrophy of the glandular substance. The new-formed connective tissue is mostly in the form of a dense, fully-formed fibrous tissue, but there are areas in which the thyroid tissue is infiltrated with small, round, lymphoid cells, apparently representing a recent infiltration. There is an increase in the elastic tissue. The gland substance shows varying degrees of compression. In some places it has almost entirely disappeared over quite wide areas; in other places it is apparently but little affected. There is an abundance of colloid material in the slightly affected areas. *Microscopic Diagnosis.*—Chronic interstitial thyroiditis.

This case is not introduced into this series to raise the question of the relation of the thyroid to the condition of scleroderma, but as a typical illustration of the pathologic changes produced in the gland by a chronic inflammatory process. Acute inflammation of the thyroid gland frequently occurs following acute general infections, as typhoid and the exanthemata. The chronic form is very often associated with other thyroid affections, the hypertrophies, cysts and tumors, and they present in varying degrees the condition here described.

VIII.—TUBERCULOSIS. TWO CASES—ONE MALE, ONE FEMALE.

No.	Age of onset.	Age at operation.	Duration.
1....................	40	42	2 yrs
2....................	35	43	8 "

In the first case the previous health of the patient was said to have been good, but death from pulmonary tuberculosis occurred six years after the operation. In the second case the history at about the time of the onset of the thyroid involvement suggested pulmonary tuberculosis. The patient now (two years after operation) is in good health and presents no evidences of active tuberculous disease in any organ.

Case XXII.—(Path. No. 64-2.) This case I am able to report as tuberculosis of the thyroid only upon clinical evidence, as although the microscopic sections show tuberculous granulation tissue no thyroid structure can be made out. The patient was a male, aged 42. The disease began two years before with a small "lump" in the region of the thyroid gland which gradually increased to the size of a walnut, suppurated and discharged spontaneously, leaving two small sinuses which have persisted for a year. At the operation by Dr. Macdonald the sinus tracts were found to lead down to the thyroid gland and they were excised together with the gland in one mass. Clinically, as recently related to me by the operator the process had its origin in the thyroid gland.

Pathology.—Macroscopic Examination: The specimen consists of a piece of tissue about one-half the size of a hen's egg. It contains some tissue which is presumably thyroid gland, and leading into it from the surface of the specimen are two sinus tracts, the walls of which aro extremely ragged and lined with yellowish purulent material. *Bacteriologic examination* fails to show tubercle bacilli.

Microscopic Examination.—No thyroid tissue is to be seen. The section consists of connective tissue and of large areas of caseation. Surrounding these areas of caseation is typical tuberculous granulation-tissue, made up of epithelioid and lymphoid cells, and containing an occasional giant cell.

Case XXIII.—(Path. No. 64-21. History taken and physical examination made December, 1905, two years after operation.) Female, aged 45. When 14 years of age parents thought she had consumption but, if so, she recovered completely. She married at 21 and now has 7 children, all in good health. At birth of last child, 11 years ago, she had puerperal fever and was seven months in bed. After this had a severe cough, night sweats and considerable expectoration. During this illness her physician first noticed a small tumor in the median line of the neck in the region of the thyroid gland which gradually increased till 2 years ago, when it reached the size of a hen's egg. It was tender on pressure and sometimes painful and caused some dyspnœa during the last year before operation. It never showed redness or signs of inflammation. The patient entered hospital at this time for an operation for uterine myomata and she was persuaded by the surgeon to allow removal of this enlarged portion of thyroid.

Operation, November 5, 1903, by Dr. A. Vander Veer.

Pathology.—Macroscopic Examination: Specimen consists of an irregular mass of reddish brown tissue 6x4x2.5 cm., in which lies a sausage-like mass. This latter on section is found to be of a uniform consistency and of moderate firmness. Color is slate brown and deviating striæ give to the cut surface a lobulated appearance.

Microscopic Examination.—(See Fig. 5.) The thyroid tissue shows marked proliferation of alveoli, the majority of whch are massed together, making the outlines of individual alveoli indistinct, while others contain a moderate amount of colloid material. In many of the lobules are circumscribed masses of epithelioid cells with occasional giant cells and a peripheral ring of lymphocytic infiltration. But a few of the tubercles show early caseation.

Microscopic Diagnosis.—Tuberculosis of the thyroid gland.

The patient was seen in December, 1905, 2 years after operation and this note on her present condition was made: "Patient is fairly well nourished, but slightly anæmic. There is a linear scar in the median line of neck 7.5 cm. in length, extending from a little beneath the chin to the episternal notch. Aside from a little thickening and redness at its lower end the scar appears healthy. There is no apparent enlargement of any portion of the thyroid gland. Patient has no cough and states that she is in good health and able to pursue her work. Examination of the lungs reveals no evidence of disease, though the breath sounds at both apices and considerably subdued. There is no glandular enlargement anywhere."

While it is true that tuberculosis of the thyroid gland is a rare disease, from recent studies it has been demonstrated that it is not so rare as was formerly supposed. Thus P.

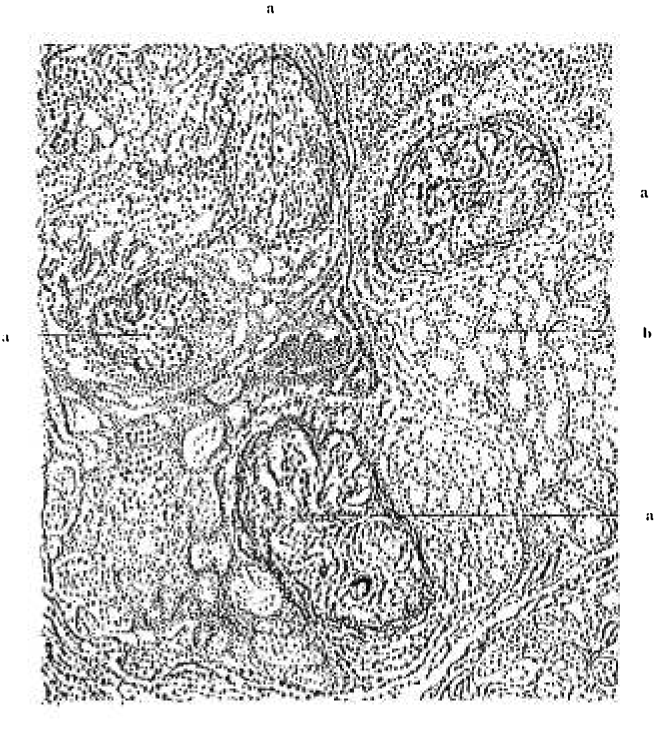

Fig. 5.—Microscopic drawing of tuberculosis of the thyroid gland, 4 oc. 3 obj. Leitz.

(a) Tubercles, in the lower one of which is seen a giant cell. In the centre of the drawing, between the tubercles, is an area of lymphocytic infiltration. (b) Normal thyroid tissue.

Bruns[3] in his report of 100 post-mortem examinations made by Chiari of persons who had suffered from tuberculosis, states that the thyroid gland was involved in seven. Of these cases 96 had suffered from chronic pulmonary tuberculosis, and in only four of these was the thyroid gland involved; the other four were cases of acute miliary tuberculosis, and in three of these the gland showed involvement. Weigert in fifty cases of chronic pulmonary tuberculosis found tuberculosis of the thyroid in six. Two forms of involvement are recognized; a miliary form secondary to a general miliary tuberculosis, and a nodular form affecting the gland diffusely. The former is the more common. It does not produce any enlargement of the organ as a rule. Of the nodular form Bruns was able to collect six cases besides his own; in three of these from a clinical point of view the thyroid lesions were primary. This form is attended by enlargement of the organ sometimes sufficient to produce pressure symptoms. As illustrated in Fig. V, these tubercules have the ordinary characteristics of tubercles in other organs. They probably always arise in the interstitial connective tissue separating the vesicles.

In the first case here recorded the data is so incomplete that no definite conclusions can be drawn. The clinical history states that the patient's previous health had been excellent, but there is no record of a physical examination to exclude a possible pulmonary involvement. Then the fact that he is said to have died 4 years later of pulmonary tuberculosis leaves us in doubt as to whether the disease was primary in the thyroid with secondary involvement of the lungs or *vice versa.*

W. B. Stanton[4] has recently made the important observation that in a comparatively large number of cases of pulmonary tuberculosis there were symptoms more or less complete of exophthalmic goitre and in these cases he has been led to examine the thyroid glands. The report is only a preliminary one and no cases in which he has observed these symptoms have died. He could not therefore give the results of histologic examination. Clinically there was slight thyroid enlargement. He records 26 cases of pulmonary tuberculosis aside from the above in which the thyroids were examined post-mortem, but in which the patients were not examined clinically for those signs. In these, tubercles were found in four. As serial sections were not made he thinks it probable that the proportion found to contain tubercles is much too small. Further investigation of this point might yield information of great value.

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[3] Beiträge zür klin. Chir., 1897, xi.

[4] American Medicine, 1905, x, 605.

IX.—CARCINOMA. ONE CASE.

Case XXIV.—(Path. No. 98-43.) Female, aged 36, with history of illness for last three years. Prominent symptoms are enlargement of thyroid gland, with pain and anæmia. The patient was operated upon two years ago for thyroid enlargement, but no pathologic study of this specimen was made.

Second operation by Dr. A. Vander Veer, February 18, 1899.

Pathology.—Macroscopic Examination: Specimen consists of six masses of tissue, all roughly lobulated and varying in size from 6 to 3 cm. in greatest diameter. They all present similar appearances and are not distinctly encapsulated, though portions of capsule are here and there evident. Where a capsule is present it is generally smooth and of a yellowish-red color. The portions of the growth which are uncovered by capsule are finely lobulated, of a light yellowish-brown color, and have a translucent appearance. This appearance suggests, in some places, the appearance of thyroid-gland tissue; in other places it has a myxomatous character. On section the nodules differ in appearance; the smaller and presumably the younger ones have an almost homogeneous yellowish-gray cut surface, which is covered by sticky mucilaginous fluid which has the glistening appearance of mucoid tissue. In one or two of the smaller masses are areas of hæmorrhage. In one rather large area of light reddish-brown tissue which does not look like hæmorrhage, there is an area homogeneous in character and slightly granular. In two of the largest nodules near the centre are areas of necrosis and calcification.

Microscopic Examination.—Sections from two different portions show an adenomatous tissue divided into irregular lobules by rather dense fibrous connective-tissue septa, which extend inward from a capsule which is present at one side. Except in a few small lobules near the periphery, where characteristic colloid-containing vesicles are seen, the tissue could not be recognized as thyroid-gland tissue. It is composed of papillomatous-like projections and long epithelial tubules with cavities of thyroid-gland spaces. This arrangement becomes complex and branching as the process develops, until they finally fill up the cavities, producing a gland-like appearance. The epithelium rests upon no visible basement-membrane; the stroma is very scanty. In the connective-tissue septa are many solid epithelial clumps which probably represent new foci of growth.

A section from the homogeneous mass differs only in that no connective-tissue septa are seen, and the spaces are more closely packed with epithelial cells. This section also shows acute inflammation. The epithelial cell is of a high cylindrical type, varying greatly in size and shape.

Microscopic Diagnosis.—Adeno-carcinoma of thyroid gland.

From one observation of carcinoma of the thyroid no important deductions can be made except to call attention to its relative infrequency. One case in 61 thyroid affections, as indicated by this series is, however, undoubtedly too low a proportion and not borne out by the statistics from other sources. Bloodgood[5] in exactly twice the number of cases records seven of carcinoma. The most elaborate study of this condition that has appeared is by Ehrhardt,[6] who has collected 150 cases of carcinoma. Sixty-five of these occurred in men and eighty-five in women; 111 appeared between the ages of thirty and sixty. In over 50 per cent. of these cases it was definitely stated that a simple goitre preceded the development of the carcinoma, and in only a comparatively small number that it arose in a normal thyroid. This is the reverse of the condition seen in this country, probably due to the fact that we have no "goitreous districts," Ehrhardt recognizes three main varieties,—the medullary, which is the most frequent, the adeno-carcinoma, and the scirrhus. The latter is, in his experience, rare. Metastases occur early as a rule. In nine-four bodies examined metastases were found in all but fourteen. In forty-six cases twenty-three had metastasized by the blood-stream alone, nine by the lymphatics alone, and fourteen by both these channels. As to the location of metastases, the lungs and bones are the most frequent seats. The bones of the skull and inferior maxilla are most commonly involved, though the sternum and long-pipe bones do not escape.

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[5] Surgery, Gynecology and Obstetrics, 1905, i, 113.

[6] Beiträge zür klin. Chir., 1902, xxxv, 343.

The average duration is about 2 years, the scirrhus form being the most chronic.

Clinical Diagnosis of Thyroid Affections.—When we bear in mind that the symmetrical enlargement of the thyroid gland indicates a hypertrophy, and the asymmetrical a tumor or a cyst, we have gone a great way towards making a diagnosis. To characterize all of the enlargements of the thyroid as "goitre" is obviously improper, as it conveys no intelligent clinical or pathologic meaning. If this term is used, it should apply to the hypertrophies, and we can then properly speak of the simple goitre and the exophthalmic goitre. To differentiate these latter conditions clinically is not difficult, for in exophthalmic goitre the subjective symptoms are definite and constant. In the simple form the rule is a much greater increase in the size of the gland but no symptoms except those produced locally by pressure. The age of onset and the duration of the disease are also important aids in diagnosis, as has been shown in the preceding tables. In the simple hypertrophy the age of onset in a large proportion of cases is before twenty. In an accurately recorded history I believe it would be exceptional to establish an onset after twenty-five. In the exophthalmic variety an onset before twenty is extremely rare; the majority of cases appear between the ages of twenty and thirty. The duration of the disease in the simple form is much longer, often twenty or thirty years, while that of the exophthalmic hypertrophy is usually less than two years. Where these two conditions are associated, or where the exophthalmic hypertrophy appears secondary to other thyroid affections, greater variation in these respects is seen. We must bear in mind that in either form of hypertrophy the process in one lobe may have advanced further than in the other, producing an asymmetrical enlargement, but on the other hand no part of the gland appears normal. In other words the process is a diffuse but not always an uniform one. Again, we have seen in certain cases a fairly symmetrical enlargement produced by an adenoma or cyst in either lateral lobe. These multiple tumors are comparatively rare, however, and on close examination present distinctive features. Of the tumors, the cysts and the adenomata are the most frequent, and they are often very difficult to differentiate. They both present the features of encapsulated tumors. The cysts are more apt to be smooth and ovoid in shape, while definite lobulations can often be made out in the adenomata. Variation in the size of the tumor seems to be frequent in the case of cysts. In regard to the recurrent adenomata, two of our observations at least would point to their being of a mild type of malignancy. Considering the long duration, however, and the fact that no metastases occurred, they do not present the features of carcinoma of the thyroid. In one case a secondary growth appeared in the region of the primary one.

From the fact that metastases of the thyroid tissue occurs in cases in which no primary tumors of the gland has been noted, bone tumors looked upon as primary should be approached with this possibility in mind.

Early diagnosis of the carcinomata presents the greatest difficulties and obviously is of the greatest importance. Age here is to be considered as indicated by the statistics of Ehrhardt. The disease is usually of short duration, a few months to one or two years. As met with in this country, carcinoma of the thyroid does not produce a large tumor, but it rapidly infiltrates the gland and surrounding tissue and dyspnœa and dysphagia are early symptoms and out of proportion to the size of the growth. Change in the voice is also an early observation (Bloodgood). In districts where simple hypertrophy is endemic a very large proportion of the cases of carcinoma, as recorded by Ehrhardt, are secondary to this condition. Here the important feature is a sudden increase in size in the hypertrophied organ, with the return of symptoms after a quiescence of perhaps many years. Primary sarcoma of the thyroid is a rare affection and as no cases were observed in our series the condition will not be discussed.*

Treatment.—As the symptoms in the uncomplicated cases of simple hypertrophy and benign tumors are of a mechanical nature, the severity of these symptoms has been our guide in treatment. Rarely is operation undertaken for the relief of the deformity alone. I believe, however, that since so large a number of these cases undergo secondary changes in later life, making operation imperative, that they should be considered upon the same basis as similar lesions in other organs. In the case of the tumors and cysts an early operation is advocated. With the simple hypertrophy, if the patient has passed young adult life, the period when we might expect a subsidence of the process, and the gland continues to enlarge, a portion of it should be removed. If after a quiescent period new growth is observed, operation may be necessary for the relief of urgent pressure symptoms, and here, too, carcinoma must be considered. Scarcely fifty years have passed since Dieffenbach considered thyroidectomy a rash undertaking. To Kocher more than anyone else is due the credit of the advances in this field of surgery. At the German Surgical Congress, in 1900[7], he reported the results of his second thousand cases of thyroidectomy, of which 929 were upon cases of simple hypertrophy and benign tumor. He had only four deaths, giving a mortality of 0.4 of 1 per cent. The greatest single factor contributing to this low mortality-rate was undoubtedly the substitution of local for general anæsthesia.

The general prinicples which guide us in the treatment of carcinoma of other organs should apply here, remembering that metastases occur early. Operation to effect a cure must be undertaken before there is extensive invasion of the surrounding tissues.

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* For report of cases and statistics see Lartigau (Amer. Jour. Med Sciences, 1901, cxxii, 156).

[7] Archiv. für klin. Chir., 1900, lxiv, 454.

In the treatment of exophthalmic goitre the various drugs and methods employed are almost innumerable. The weight of opinion now seems to favor partial thyroidectomy, and I believe justly so, for with the accumulating statistics the percentage of cures is increasing and the number of primary deaths decreasing. No other form of treatment has offered so much hope. The observations in this series have been made entirely on the operative treatment, but to give an opportunity for comparison I may be allowed to quote from a review of the literature made recently by the writer,[8] in which the results of some of the other more recent methods of treatment are recorded. "In late years attempts have been made in many German clinics to develop a specific treatment of exophthalmic goitre." Lanz,[9] as early as 1894, began the use of the milk of thyroidectomized goats in patients with Graves's disease. He has recently recorded favorable results in five cases. Burghart and Blumenthal[10] in Leyden's clinic have injected the blood-serum of amyxo-œdematous patients into those suffering from exophthalmic goitre. Leyden reviews their results and thinks they are encouraging. Later, in this clinic, was introduced the use of a precipitate from the milk of thyroidectomized goats, called "rodagin." A few cases are recorded of slight improvement after continued use of this substance. Kollaritis reports no improvement in three cases in which he employed this method.

Moebius and Schultes[11] have used the serum of thyroidectomized sheep. This serum is called *antithyroidin.* Moebius reports three cases somewhat improved by this treatment and later two other cases which were benefited. Schultes and Rosenfield have likewise each reported a case. In a recent communication Moebius[12] speaks rather guardedly of the employment of this serum. Kuh,[13] after treating eleven cases with the serum, is unwilling to make any statement as to its curative effect. He thinks it relieved nervousness and diminished tachycardia.

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[8] Albany Med. Annals, 1906, xxvii, 111.

[9] Münch. Med. Wochenschr., 1903, l, 146.

[10] Deutsche med. Wochenschr., 1899, xxv, 627.

[11] Münch. med. Wochenschr., 1901, xviii, 1873.

In regard to the operative treatment, in four of our six cases the partial excision of the thyroid gland has been attended with excellent results. In two of these all the symptoms have been relieved; in one the operation was of too recent date to determine the ultimate result, but the symptoms one month after operations improved in all respects; in the other all the symptoms except exophthalmus had disappeared, and the patient is able to pursue her work. The time now intervening since operation varies from one month to four years, as shown in the table. Of the two deaths one could be ascribed to the anæsthetic, and the other, in which death took place on the eighth day with the symptoms of extreme hyperthyroidization, as a late case probably beyond possible recovery. It should be borne in mind that the operative treatment, to be of the most value, should be undertaken early, before damage has been done to the nervous system. In this condition even more than in other forms of thyroid affections, the importance of local anæsthesia cannot be too highly estimated. As further proof of the superiority of the operative treatment, the statistics of a number of observers are quoted. The best results of partial thyroidectomy yet published are those of Kocher—59 cases: 75 per cent. cured; 17 per cent. improved; 6.7 per cent. dead.

At the last German Surgical Congress, April, 1905, Friedheim from the clinic of Kümmel reported the results of twenty cases of partial thyroidectomy after five or more years had elapsed. Fourteen were cured, two much improved, three slightly improved, and one had died. In seven of the cured cases the operation had been performed nine or more years previous; in one, fifteen and a-half years. He further presents the statistics of the other large German clinics for the last years as follows:

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[12] Münch. med. Wochenschr., 1903, l, 146.

[13] Medicine, 1905, xi, 672.

	Cases.	Cured.	Improved.	Dead.
Von Mikulicz	18	10	7	1
Krönlein	24	16	6	2
Kocher	59	45	10	4
König	8	4	..	1